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Title Page

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DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RATS

Sponsor: U.S. Army Medical Materiel Development Activity

Test Article: WR242511 Tartrate

Contract No.: DAMD17-92-C-2001

Study Director

Barry S. Levine, D.Sc., D.A.B.T.

In-Life Phase Completed On

May 6, 1994

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This dose range-finding study evaluated the developmental toxicity of WR242511 tartrate in time-mated CD® female rats. Doses were 0, 0.5, 1, 2, 4 and 8 mg base/kg/day administered by gavage during gestation days (GD) 6 - 15 (GD0 = day of vaginal plug). Maternal toxicity was observed at the high dose as a significant decrease in total weight gain. In addition, significant decreases in mean daily food consumption were seen during the treatment period. Rough coat was also observed in three females during GD13-15. The 4 mg base/kg/day dose was considered near or at the maternal no observable effect level (NOEL).

Fetal toxicity was apparent at 8 mg base/kg/day as significant decreases in body weights were seen. At the 4 mg base/kg/day dose, a biologically significant decrease in fetal mean body weights was observed, but was only statistically significant in female fetuses. However, at 1 mg base/kg/day a statistically significant decrease was present in both sexes. No biological differences in any other fetal parameters were observed at the high dose or mid high dose groups vs. the control group. The absence of an effect on fetal body weights at 2 mg base/kg/day could not be explained. Fetal body weight changes at 8 mg base/kg/day were considered due to and/or associated with maternal toxicity. The 1 mg base/kg/day dose was considered at or near the low observable adverse effect level (LOAEL) for fetal toxicity. Accordingly the following doses are recommended for the definitive developmental toxicity (Segment II) study in rats: 0, 0.5, 2 and 8 mg base/kg/day.

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Signature Page

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RATS

TRL Chemical No.: 1720614

Sponsor: U.S. Army Medical Materiel
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Fort Detrick
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Test Article: WR242511 Tartrate

Sponsor
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Testing Facility: TOXICOLOGY RESEARCH LABORATORY (TRL)
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Barry S. Levine, D.Sc., D.A.B.T. Study Director	Date	Ashraf F. Youssef, M.D., Ph.D. Reproductive Toxicologist	Date

In-life Phase Initiation: April 14, 1994

Dosing Initiation: April 21, 1994

In-Life Completion: May 6, 1994

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1. SUMMARY

This dose range-finding study evaluated the developmental toxicity of WR242511 tartrate in time-mated CD® female rats. Doses were 0, 0.5, 1, 2, 4 and 8 mg base/kg/day administered by gavage during gestation days (GD) 6 - 15 (GD0 = day of vaginal plug). The results of maternal and fetal toxic responses are summarized in Table 1. Maternal toxicity was observed at the high dose as a significant decrease in total weight gain. In addition, significant decreases in mean daily food consumption were seen during the treatment period. Rough coat was also observed in three females during GD13-15. The 4 mg base/kg/day dose was considered near or at the maternal no observable effect level (NOEL).

Fetal toxicity was apparent at 8 mg base/kg/day as significant decreases in body weights were seen. At the 4 mg base/kg/day dose, a biologically significant decrease in fetal mean body weights was observed, but was only statistically significant in female fetuses. However, at 1 mg base/kg/day a statistically significant decrease was present in both sexes. No biological differences in any other fetal parameters were observed at the high dose or mid high dose groups vs. the control group. The absence of an effect on fetal body weights at 2 mg base/kg/day could not be explained. Fetal body weight changes at 8 mg base/kg/day were considered due to and/or associated with maternal toxicity. The 1 mg base/kg/day dose was considered at or near the low observable adverse effect level (LOAEL) for fetal toxicity. Accordingly the following doses are recommended for the definitive developmental toxicity (Segment II) study in rats: 0, 0.5, 2 and 8 mg base/kg/day.

2. INTRODUCTION

This study was conducted to provide information for use in the selection of dose levels for a developmental toxicity study in rats. The test article was administered by daily gavage to time-mated females during gestation days 6 - 15. The fetuses were delivered by Cesarean section on gestation day 20 and were examined grossly for abnormalities. All methods and procedures in this study were conducted within the spirit of the Toxicology Research Laboratory, University of Illinois at Chicago Quality Assurance Program designed to conform with FDA Good Laboratory Practices Regulations. No unforeseen circumstances affected the integrity of the study. This study was stagger-started over two days and was initiated on the night of April 14, 1994 (initiation of mating). Dosing was initiated (stagger-started) on April 21, 1994 (GD6) and the in-life portion was terminated on May 6, 1994 (GD20).

3. MATERIALS AND METHODS

3.1 Test Article

WR242511 tartrate (Bottle Lot No. BM 05816), a fine, yellow powder, was received on June 16, 1993 from Herner & Co. for this study, and was previously assigned an in-house chemical number (1720614). The chemical name of the test article is 8-[(4-Amino-1-methylbutyl)amino]-5-(1-hexyloxy)-6-methoxy-4-methylquinoline DL-tartrate and the mole fraction of the base is 0.71. It was stored at -20 to -15°C and ambient humidity in the freezer, and was protected from light (the container was wrapped in aluminum foil).

3.2 Animals

Forty-two female Virus Antibody Free (VAF) CD® rats were obtained from Charles River Breeding Laboratories, Portage, MI on April 18, 1994. The animals were 61 days old upon arrival at the UIC AAALAC-accredited animal facility (date of birth 02/16/94). Each animal was given a study-unique number (ear-tag) by the supplier. This number appeared on a cage card visible on the front of each cage. The cage card additionally contained the study number, test article identification, treatment group number, and dose level. Cage cards were color-coded as a function of treatment group. Animals were singly housed in polycarbonate cages with Anderson Bed-a-cob bedding (Heinhold Co., Kankakee, IL) in a temperature (65-78°F) and humidity (approx. 30-70 %) controlled room with a 14 hour light/10 hour dark cycle. The cage size, 840 cm^2 area and 20 cm height, was adequate to house rats at the upper weight range as described in the *Guide for the Care and Use of Laboratory Animals*, DHHS (NIH) No. 86.23. All animals were routinely transferred to clean cages with fresh bedding weekly.

Certified Rat Chow No. 5002 (PMI Feeds, Inc., St. Louis, MO) and tap water from an automatic watering system in which the room distribution lines were flushed daily were provided *ad libitum* from arrival until termination. The water was untreated with additional chlorine or HCl. There are no known contaminants in the feed or water which were expected to influence the study. The results of the most current comprehensive chemical analyses of Chicago water are documented in files maintained by Quality Assurance.

3.3 Experimental Design

Animals were mated on two sequential nights at the supplier's facility. The morning when the vaginal plug was found was considered gestation day 0 (GD0). At each GD0, 20 females showing vaginal plugs were collected. The body weights on GD0 were obtained by the supplier after balance standardization. Each animal was ear tagged by the supplier. Of the 40 presumed pregnant rats which were received, 20 were at GD2 and the other 20 were at GD3 upon arrival at the animal facility. All animals were quarantined at least for 3 days before initiation of dosing (GD6). All animals were examined daily during the quarantine period, and were approved for use by the Clinical Veterinarian prior to being placed on test. Fifteen animals from each gestation day 0 subset were randomized into six groups on the basis of body weight to result in 5 animals/group.

Dose levels were selected on the basis of a two week oral toxicity study and a thirteen week oral toxicity study in rats (UIC/TRL Study Nos. 106 & 107, respectively) as follows:

Group No.	Dose Level (mg base/kg/day)	Number of Females*
1	0	5
2	0.5	5
3	1.0	5
4	2.0	5
5	4.0	5
6	8.0	5

* Presumed Pregnant

The test article was administered by gavage once daily during gestation days 6 through 15. The gavage procedure was accomplished by the use of a rigid oral feeding needle. The dosing suspensions were administered at a dosing volume of 5 ml/kg. A stock test article suspension was prepared weekly by suspending the appropriate quantity of the test article in the vehicle (aqueous 1% Methylcellulose/0.2% Tween 80). Daily dosage formulations were prepared by diluting the stock to the appropriate concentration(s). The stock and dosing suspensions were kept at 0-4°C. Since this study is not GLP compliant, analytical chemistry analyses were not performed on the dosage formulations. Data from previous studies (UIC/TRL Nos. 106 and 107) showed that the stock formulation and dosing suspensions were stable at least for two weeks and two days, respectively. In addition, several dosing suspensions in one of those studies demonstrated homogeneity, i.e.coefficient of variation between top, middle and bottom was less than 4% (UIC/TRL Study No. 107).

Non-fasted body weights were recorded on gestation day 0 (GD0 by the supplier), GD4 (for randomization), and on GD6-15, GD18 and GD20. Food consumption for all animals was measured during the following intervals: GD6-10, GD10-15 and GD15-20. Clinical signs were observed and recorded approximately 1 - 2 hours post-dosing on the days of dosing and in each morning after completion of the dosing period. Animals were also observed for moribundity/mortality immediately prior to dosing and in the afternoon (after at least six hours), and in the afternoon after dosing ceased.

On GD20, all rats were killed in random order by carbon dioxide asphyxiation. The abdominal and thoracic cavities were opened by a ventral midline incision. The uterus was examined and weighed. In gravid animals, the number of *corpora lutea* on each ovary was recorded and the ovaries were discarded after evaluation. The viability of the fetuses were checked *in utero*. A viable fetus was defined as one which responds to stimuli. A non-viable fetus was defined as a term fetus which does not respond to stimuli *in utero* or is not breathing. The number and location of fetuses, early resorption(s), late resorption (s) and the total number of implantation sites and their uterine distribution were documented using the following procedure. All implantation sites, including resorptions, were numbered in consecutive fashion beginning with the left distal uterine horn, and similarly numbered from the proximal to the distal right uterine horn. An early resorption was defined as one in which it is not grossly evident that organogenesis has occurred. A late resorption was defined as one in which it was grossly evident that organogenesis had occurred. A fetus with evident autolysis was considered a late resorption. Following the cesarean section examination, the carcass of each dam was discarded.

Fetuses were weighed, sexed, and euthanized by sodium pentobarbital (400 mg/ml), $\approx$ 0.04 ml/fetus I.P., and examined for gross external alterations. If abnormalities were noted, the fetuses were preserved in Bouin's solution as deemed necessary. All other fetuses were discarded.

The uterus from a female that appeared nongravid was opened and placed in 0.5% ammonium sulfide solution for at least 10 minutes for detection of possible implantation sites. If implantation sites were detected, ovaries were evaluated as previously mentioned.

3.4 Statistical Analyses:

The incidences or the means and standard deviations of the maternal and fetal observations were calculated. Statistical analysis of fetal body weights considered the fetus as the unit of measure. Only data from gravid animals were included in the data analyses. Fetal body weights, maternal body weights and weight gains, uterine relative weight (% body weight) and food consumption data were analyzed by Analysis of variance tests. If a significant F ratio was obtained ($p \leq 0.05$), Dunnett's test was used for pair-wise comparisons to the control group.

The number of implantation sites, *corpora lutea*, early and late resorptions, viable fetuses, percent of pre-implantation loss, percent of post-implantation loss, and total losses were compared across groups using the Kruskal-Wallis nonparametric ANOVA test. If a significant effect occurred ($P \leq 0.05$), the Mann-Whitney U test was used for pair-wise comparisons to the control group.

Calculations were as follows:

Pre-implantation loss % = [(#*Corpora lutea* - # Implants)/ # *Corpora lutea*] x 100
Post-Implantation loss % = [(#Implants - # Viable fetuses)/ #Implants] x 100
Total loss/litter % = [(#*Corpora lutea* - # Viable fetuses)/ # *Corpora lutea*] x 100

4. RESULTS

4.1 Mortality/Clinical Observations

The summary of clinical signs of toxicity is in Table 2. Individual signs are in Appendix 1.

No animal died in this study. Rough coat was seen in three females at 8 mg base/kg/day. This sign was observed towards the end of the dosing period (i.e. GD13-15), and was not apparent in the lower dose levels.

4.2 Maternal Body Weights

The summaries of maternal body weights and weight gains are in Tables 3 and 4, respectively. Individual data are included in Appendix 1.

All animals gained weight during GD0-6. Upon initiation of dosing on GD6, high dose animals essentially failed to gain weight during the treatment period. These high dose animals subsequently gained more weight than animals in the other treatment groups during GD15-18 (i.e. after cessation of treatment). Total body weight gain for the high dose animals, however, was significantly less than control animals. Body weights were not affected in the other dose levels.

4.3 Food Consumption

The summary of mean daily food consumption is in Table 5. Individual food consumption data are shown in Appendix 1.

Only high dose pregnant females showed significant decreases in food consumption during dosing (i.e. during the periods GD6-10 and GD10-15). Food consumption was not affected in these animals after cessation of treatment or in the lower dose levels.

4.4 Cesarean-Section Observations

The summary of the cesarean section data is in Table 6. Individual data are included in Appendix 1.

One animal at the 8 mg base/kg/day dose level was non-pregnant; all other animals demonstrated implantation sites. Treatment with WR242511 tartarate during GD6-15 did not affect fetal viability or the rate of resorption. The numbers of *corpora lutea*, early and late resorptions, implantations, pre or post implantation loss, or total loss/litter were not significantly different between drug-treated and control animals.

4.5 Fetal Observations

The summary of fetal observations is in Table 7. The summary of fetal body weights is in Table 8. Individual data are included in Appendix 2.

Fetal body weights were significantly reduced at 8 mg base/kg/day. Although slight, but statistically significant reductions in fetal body weight were also seen at the 1 and 4 mg base/kg/day dose levels, no significant reduction was seen in maternal body weights (Table 3). This indicated the potential for direct developmental toxicity. While similar decreases in fetal body weights were not observed at 2 mg base/kg/day, statistically significant decreases in fetal body weights (both sexes) were observed at the 1 mg base/kg/day dose level. Normal variations consisting of subcutaneous hematomas and scattered petechial hemorrhages were observed in all doses and in the control group, and were considered biologically insignificant.

5. DISCUSSION

This study evaluated limited developmental toxicity data for WR242511 Tartrate in CD® pregnant rats when administered by gavage during gestation days 6-15. Doses were 0, 0.5, 1, 2, 4 and 8 mg base/kg/day. The results of this study are to be used to aid in the selection of dose levels for a developmental toxicity study in this species, and are summarized in Table 1.

Maternal toxic manifestations included significant decreases in body weights and food consumption at the 8 mg base/kg/day dose. In addition, rough coat was seen in three high dose dams towards the end of the dosing period. Fetal toxicity was manifested as significant decreases in body weight but without any increase in abnormalities, incidence of resorptions or decrease in fetal viability. While marginal fetal toxicity was manifested at 1, 4 and 8 mg base/kg/day, the absence of an overt effect on the fetuses at 2 mg base/kg/day was noted. It is suggested that the dose levels for the definitive developmental toxicity (Segment II) study

should not exceed 8 mg base/kg/day and should include one dose level less than 1 mg base/kg/day. Accordingly, doses suggested for the definitive developmental toxicity study are as follows: 0, 0.5, 2 and 8 mg base/kg/day.

6. PERSONNEL

Study Director	Barry S. Levine, D.Sc., D.A.B.T.
Reproductive Toxicologist	Ashraf F. Youssef, M.D., Ph.D.
Reproductive Scientist	Roberto A. Matamoros, D.V.M., Ph.D.
Clinical Veterinarian	James E. Artwohl, D.V.M., M.S., D.A.C.L.A.M.
Veterinarian Support	Documented in raw data
Tox. Lab Supervisor	Soudabeh Soura, B.S.
Lead Technician	Nancy Dinger, B.S.

Report preparation is assisted by Dr. Ashraf Youssef, Ms. Soudabeh Soura and Ms. Rae Jean Ballentine.

7. ARCHIVES

All raw data, documentation, specimens, test article reserves, and the final report are archived at the University of Illinois at Chicago, Toxicology Research Laboratory, Department of Pharmacology, Chicago, IL 60612.

Table 1

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RATS

Summary of Toxic Responses

Dose Level (mg base/kg/day)	0.0	0.5	1.0	2.0	4.0	8.0
Number of litters	5	5	5	5	5	4[a]
Clinical signs	-	-	-	-	-	RC
Decrease in maternal body weight gain	-	-	-	-	-	+
Decrease in daily mean food consumption	-	-	-	-	-	+
Decrease in fetal body weight (♀/♂)	-/-	-/-	+/+	-/-	+/-	+/+

RC = Rough Coat
- = Absent
+ = Present
[a]One female was not pregnant

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DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL SIGNS

STUDY: 143 SEX: FEMALE

DOSE: (mg base/kg)	0	0.5	1.0	2.0	4.0	8.0
GROUP:	1-F	2-F	3-F	4-F	5-F	6-F
Scheduled Sacrifice	5	5	5	5	5	5
Rough Coat	0	0	0	0	0	3
Total Number of Animals	5	5	5	5	5	5

Table 3

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RATS

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 143 SEX: FEMALE

PERIOD	DOSE: (mg base/kg) GROUP:	0 1-F	0.5 2-F	1.0 3-F	2.0 4-F	4.0 5-F	8.0 6-F
DAY 0	MEAN	215	219	219	217	215	212
	S.D.	5.3	4.5	5.9	7.9	7.2	4.8
	N	5	5	5	5	5	4
DAY 4	MEAN	226	227	228	227	226	224
	S.D.	6.2	4.9	6.2	8.9	4.5	6.8
	N	5	5	5	5	5	4
DAY 6	MEAN	243	245	246	247	245	243
	S.D.	7.6	4.6	5.1	9.7	6.9	6.7
	N	5	5	5	5	5	4
DAY 7	MEAN	247	251	250	253	247	244
	S.D.	8.9	6.5	5.1	8.2	10.1	10.1
	N	5	5	5	5	5	4
DAY 8	MEAN	252	257	254	260	255	241
	S.D.	9.6	6.1	7.2	8.4	11.2	9.6
	N	5	5	5	5	5	4
DAY 9	MEAN	255	263	258	267	259	238*
	S.D.	9.9	7.6	5.2	9.1	12.2	9.5
	N	5	5	5	5	5	4
DAY 10	MEAN	262	270	264	272	262	240*
	S.D.	5.5	8.4	4.7	7.4	8.2	7.5
	N	5	5	5	5	5	4
DAY 11	MEAN	269	276	269	277	266	240*
	S.D.	8.1	8.7	6.0	10.5	8.4	7.3
	N	5	5	5	5	5	4
DAY 12	MEAN	277	279	273	283	271	240*
	S.D.	10.2	10.6	4.8	11.1	13.5	7.5
	N	5	5	5	5	5	4
DAY 13	MEAN	282	285	279	288	275	237*
	S.D.	10.6	12.4	6.9	9.7	16.5	8.7
	N	5	5	5	5	5	4

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RATS

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 143 SEX: FEMALE

PERIOD	DOSE: (mg base/kg) GROUP:	0 1-F	0.5 2-F	1.0 3-F	2.0 4-F	4.0 5-F	8.0 6-F
DAY 14	MEAN	290	293	284	298	279	239*
	S.D.	12.5	9.0	9.0	8.5	13.8	6.7
	N	5	5	5	5	5	4
DAY 15	MEAN	302	298	296	306	289	249*
	S.D.	12.6	12.4	11.5	7.4	14.1	11.3
	N	5	5	5	5	5	4
DAY 18	MEAN	338	329	330	344	329	299*
	S.D.	16.1	16.7	15.2	12.1	17.0	16.2
	N	5	5	5	5	5	4
DAY 20	MEAN	369	357	355	375	353	329*
	S.D.	17.5	22.3	19.6	13.4	18.8	21.5
	N	5	5	5	5	5	4

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

Table 4

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RATS

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 143 SEX: FEMALE

PERIOD [a]	DOSE: (mg base/kg) GROUP:	0 1-F	0.5 2-F	1.0 3-F	2.0 4-F	4.0 5-F	8.0 6-F
DAY 7 [b]	MEAN	4	5	4	6	2	1
	S.D.	2.9	1.9	1.1	2.9	4.0	3.8
	N	5	5	5	5	5	4
DAY 8	MEAN	5	6	5	7	8	-3*
	S.D.	3.7	4.1	2.6	3.2	3.2	3.1
	N	5	5	5	5	5	4
DAY 9	MEAN	3	6	3	7	4	-3
	S.D.	3.8	4.8	7.9	1.5	3.8	10.1
	N	5	5	5	5	5	4
DAY 10	MEAN	7	7	6	5	3	2
	S.D.	5.8	2.3	4.0	4.2	4.9	2.2
	N	5	5	5	5	5	4
DAY 11	MEAN	7	6	5	5	4	-1
	S.D.	2.9	1.4	1.9	4.1	3.1	7.4
	N	5	5	5	5	5	4
DAY 12	MEAN	7	4	4	6	6	0
	S.D.	2.7	2.3	5.1	5.0	5.1	0.5
	N	5	5	5	5	5	4
DAY 13	MEAN	5	6	6	5	3	-3
	S.D.	1.5	2.2	4.2	2.9	4.0	8.4
	N	5	5	5	5	5	4
DAY 14	MEAN	8	9	5	10	4	2
	S.D.	4.2	3.8	2.9	4.0	3.4	5.0
	N	5	5	5	5	5	4
DAY 15	MEAN	11	4*	12	7	10	10
	S.D.	3.1	4.8	3.1	3.6	1.2	5.2
	N	5	5	5	5	5	4
DAY 18	MEAN	36	32	34	38	40	50*
	S.D.	4.2	6.6	6.1	5.9	5.1	5.8
	N	5	5	5	5	5	4

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

a = Successive periods

b = Baseline is Day 6

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY STUDY OF WR242511 IN RATS

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 143 SEX: FEMALE

PERIOD [a]	DOSE: (mg base/kg) GROUP:	0 1-F	0.5 2-F	1.0 3-F	2.0 4-F	4.0 5-F	8.0 6-F
DAY 20 [b]	MEAN	30	28	26	31	24	30
	S.D.	1.8	6.7	4.9	2.5	5.5	8.3
	N	5	5	5	5	5	4
TOTAL GAIN	MEAN	126	111	110	128	108	86*
	S.D.	13.2	20.1	20.6	8.6	16.4	16.3
	N	5	5	5	5	5	4

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

a = Successive periods
b = Baseline is Day 6

Table 5

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RATS

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 143 SEX: FEMALE

PERIOD [a]	DOSE: (mg base/kg) GROUP:	0 1-F	0.5 2-F	1.0 3-F	2.0 4-F	4.0 5-F	8.0 6-F
DAY 10 [b]	INTAKE (g)	19	20	19	20	18	13*
	S.D.	1.5	2.4	1.1	0.9	2.6	3.0
	N	5	5	5	5	5	4
DAY 15	INTAKE (g)	23	23	23	25	20	14*
	S.D.	1.7	1.3	1.2	2.1	2.3	3.9
	N	5	5	5	5	5	4
DAY 20	INTAKE (g)	25	24	25	27	25	25
	S.D.	1.6	3.4	3.2	1.1	2.2	4.1
	N	5	5	5	5	5	4

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

a = Successive periods

b = Food in on Day 6

Table 6

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY STUDY OF WR242511 IN RATS

Summary of Maternal Cesarean Section Data
(Mean ± S.D.)

Dose level (mg base/kg/day)	0.0	0.5	1.0	2.0	4.0	8.0
Total Number of Females/Group	5	5	5	5	5	5
Total Number of Surviving Females	5	5	5	5	5	5
Total Number of Pregnant Females	5	5	5	5	5	4
Uterine Weight (% Body Weight)	19.8 ± 0.9	16.8 ± 3.4	18.8 ± 1.2	18.2 ± 1.5	19.3 ± 1.7[a]	20.7 ± 3.4
Implantation Sites	13.0 ± 1.3	12.0 ± 0.9	12.6 ± 1.0	12.6 ± 0.5	12.6 ± 1.2	13.3 ± 0.8
Corpora Lutea	16.0 ± 2.3	16.0 ± 1.4	15.8 ± 1.6	16.8 ± 1.2	15.8 ± 3.2	16.0 ± 2.3
Early Resorptions	0.6 ± 0.8	1.8 ± 1.3	0.8 ± 0.4	1.0 ± 0.6	0.2 ± 0.4	1.0 ± 1.2
Late Resorptions	0	0	0	0	0	0
Viable Fetuses	12.4 ± 0.8	10.6 ± 2.1	11.8 ± 1.0	11.6 ± 0.8	12.4 ± 0.8	12.3 ± 1.9
Pre-Implantation Loss %[b]	16.4 ± 17.7	24.6 ±7.3	19.9 ± 5.7	24.7 ± 5.4	20.2 ± 18.0	16.1 ± 8.6
Post-Implantation Loss %[c]	4.2 ± 5.5	12.2 ± 13.4	6.3 ± 3.2	8.0 ± 4.9	1.3 ± 2.7	8.0 ± 10.2
Total Loss / Litter %[d]	20.7 ± 13.2	33.6 ± 13.1	25.0 ± 4.7	30.8 ± 4.3	20.2 ± 18.0	23.1 ± 10.0

Statistical Analysis: Uterine Weight by ANOVA/Dunnett's Test, all other data by Kruskal-Wallis/Mann-Whitney U Test.

[a]N = 4
[b]Pre Implantation Loss % = [(# Corpora Lutea - # Implants)/ # Corpora Lutea] x 100
[c]Post Implantation Loss % = [(# Implants - # Viable Fetuses)/ # Implants] x 100
[d]Total Loss/Litter = [(# Corpora Lutea - # Viable Fetuses)/ # Corpora Lutea] x 100
[e]Statistically Significant ($p \leq 0.05$)

Table 7

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY
STUDY OF WR242511 IN RATS

Summary of Fetal Observations

Dose Level (mg base/kg/day)		0.0	0.5	1.0	2.0	4.0	8.0
Total # of Fetuses (# of Litters)[a]		62 (5)	53 (5)	59 (5)	58 (5)	62 (5)	49 (4)
Sex Distribution:	Males	31	29	33	26	28	29
	Females	31	24	26	32	34	20
Sex Ratio:	Males/Females %	50/50	55/45	56/44	45/55	45/55	59/41
Body Weight(g): (Mean ± S.D.)	Males	3.94 ± 0.29	3.82 ± 0.43	3.67 ± 0.36[c]	3.92 ± 0.28	3.85 ± 0.29	3.66 ± 0.48[c]
	Females	3.92 ± 0.29	3.72 ± 0.42	3.58 ± 0.29[c]	3.79 ± 0.35	3.67 ± 0.28[c]	3.57 ± 0.46[c]
Number of Normal Fetuses (%)		40 (64.5)	42 (79.2)	43 (72.9)	50 (86.2)	49 (79.0)	44 (89.8)
Number of Fetuses with Variations[b]		22	11	16	8	13	5

[a]All fetuses were viable
[b]Hematoma or Petechial Hemorrhage (normal variations)
[c]Statistically Significant by ANOVA/Dunnett's Test ($p \leq 0.05$)

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RATS

SUMMARY OF BODY WEIGHTS (Grams) (Fetal)

STUDY: 143L SEX: MALE

PERIOD	DOSE: (mg base/kg) GROUP:	0 1-M	0.5 2-M	1.0 3-M	2.0 4-M	4.0 5-M	8.0 6-M
DAY 20	MEAN	3.94	3.82	3.67*	3.92	3.85	3.66*
	S.D.	0.290	0.430	0.360	0.281	0.290	0.482
	N	31	29	33	26	28	29

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RATS

SUMMARY OF BODY WEIGHTS (Grams) (Fetal)

STUDY: 143L SEX: FEMALE

PERIOD	DOSE: (mg base/kg) GROUP:	0 1-F	0.5 2-F	1.0 3-F	2.0 4-F	4.0 5-F	8.0 6-F
DAY 20	MEAN	3.92	3.72	3.58*	3.79	3.67*	3.57*
	S.D.	0.289	0.420	0.291	0.354	0.279	0.463
	N	31	24	26	32	34	20

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

APPENDIX 1

INDIVIDUAL MATERNAL DATA

- Individual Observations
- Individual Body Weights
- Individual Weight Gain
- Individual Daily Food Consumption
- Individual Uterine Weights
- Individual Maternal Cesarean Section Data

INDIVIDUAL OBSERVATIONS

STUDY: 143 GROUP: 1-F SEX: FEMALE
DAY 0-DAY 21 DOSE: 0 (mg base/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
807	Normal			DAY 6-DAY 19
	Scheduled Sacrifice			DAY 20
810	Normal			DAY 6-DAY 19
	Scheduled Sacrifice			DAY 20
812	Normal			DAY 6-DAY 19
	Scheduled Sacrifice			DAY 20
830	Normal			DAY 6-DAY 19
	Scheduled Sacrifice			DAY 20
837	Normal			DAY 6-DAY 19
	Scheduled Sacrifice			DAY 20

INDIVIDUAL OBSERVATIONS

STUDY: 143 GROUP: 2-F SEX: FEMALE
DAY 0-DAY 21 DOSE: 0.5(mg base/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
803	Normal			DAY 6-DAY 19
	Scheduled Sacrifice			DAY 20
806	Normal			DAY 6-DAY 19
	Scheduled Sacrifice			DAY 20
826	Normal			DAY 6-DAY 19
	Scheduled Sacrifice			DAY 20
836	Normal			DAY 6-DAY 19
	Scheduled Sacrifice			DAY 20
842	Normal			DAY 6-DAY 19
	Scheduled Sacrifice			DAY 20

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY STUDY OF WR242511 IN RATS

INDIVIDUAL OBSERVATIONS

STUDY: 143 GROUP: 3-F SEX: FEMALE
DAY 0-DAY 21 DOSE: 1.0(mg base/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
805	Normal			DAY 6-DAY 19
	Scheduled Sacrifice			DAY 20
813	Normal			DAY 6-DAY 19
	Scheduled Sacrifice			DAY 20
821	Normal			DAY 6-DAY 19
	Scheduled Sacrifice			DAY 20
832	Normal			DAY 6-DAY 19
	Scheduled Sacrifice			DAY 20
841	Normal			DAY 6-DAY 19
	Scheduled Sacrifice			DAY 20

INDIVIDUAL OBSERVATIONS

STUDY: 143 GROUP: 4-F SEX: FEMALE
DAY 0-DAY 21 DOSE: 2.0 (mg base/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
801	Normal			DAY 6-DAY 19
	Scheduled Sacrifice			DAY 20
802	Normal			DAY 6-DAY 19
	Scheduled Sacrifice			DAY 20
827	Normal			DAY 6-DAY 19
	Scheduled Sacrifice			DAY 20
835	Normal			DAY 6-DAY 19
	Scheduled Sacrifice			DAY 20
839	Normal			DAY 6-DAY 19
	Scheduled Sacrifice			DAY 20

INDIVIDUAL OBSERVATIONS

STUDY: 143 GROUP: 5-F SEX: FEMALE
DAY 0-DAY 21 DOSE: 4.0 (mg base/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
808	Normal			DAY 6-DAY 19
	Scheduled Sacrifice			DAY 20
818	Normal			DAY 6-DAY 19
	Scheduled Sacrifice			DAY 20
819	Normal			DAY 6-DAY 19
	Scheduled Sacrifice			DAY 20
829	Normal			DAY 6-DAY 19
	Scheduled Sacrifice			DAY 20
840	Normal			DAY 6-DAY 19
	Scheduled Sacrifice			DAY 20

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY STUDY OF WR242511 IN RATS

INDIVIDUAL OBSERVATIONS

STUDY: 143 GROUP: 6-F mg base/kg SEX: FEMALE PAGE: 1
DAY 0-DAY 21 DOSE: 8.0(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
809	Normal			DAY 6-DAY 19
	Scheduled Sacrifice			DAY 20
811	Normal			DAY 6-DAY 12
	Normal			DAY 16-DAY 19
	Rough Coat			DAY 13-DAY 15
	Scheduled Sacrifice			DAY 20
828	Scheduled Sacrifice			DAY 20
831	Normal			DAY 6-DAY 12
	Normal			DAY 16-DAY 19
	Rough Coat			DAY 13-DAY 15
	Scheduled Sacrifice			DAY 20
823	Normal			DAY 6-DAY 12
	Normal			DAY 15-DAY 19
	Rough Coat			DAY 13-DAY 14
	Scheduled Sacrifice			DAY 20

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY STUDY OF WR242511 IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 143 GROUP: 1-F SEX: FEMALE
DOSE: 0(mg base/kg)

ANIMAL #	DAY 0	DAY 4	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15
807	218	233	248	248	256	256	265	274	281	288	294	307
810	208	218	231	234	242	249	261	265	274	279	282	298
812	211	229	245	250	255	263	262	269	276	279	288	298
830	216	222	240	243	242	242	254	259	262	268	278	286
837	221	230	250	258	264	266	269	280	290	296	310	320
MEAN	215	226	243	247	252	255	262	269	277	282	290	302
S.D.	5.3	6.2	7.6	8.9	9.6	9.9	5.5	8.1	10.2	10.6	12.5	12.6
N	5	5	5	5	5	5	5	5	5	5	5	5

--: Data Unavailable

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY STUDY OF WR242511 IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 143 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg base/kg)

ANIMAL #	DAY 18	DAY 20
807	345	378
810	330	360
812	337	367
830	318	346
837	361	392
MEAN	338	369
S.D.	16.1	17.5
N	5	5

--: Data Unavailable

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 143 GROUP: 2-F SEX: FEMALE
DOSE: 0.5 (mg base/kg)

ANIMAL #	DAY 0	DAY 4	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15
803	220	229	240	243	251	264	267	273	274	277	288	295
806	219	232	249	255	266	275	284	290	297	306	308	315
826	213	219	242	246	252	257	265	269	271	277	286	285
836	216	226	245	251	255	256	263	269	273	278	289	288
842	225	228	251	259	259	262	269	277	281	286	296	305
MEAN	219	227	245	251	257	263	270	276	279	285	293	298
S.D.	4.5	4.9	4.6	6.5	6.1	7.6	8.4	8.7	10.6	12.4	9.0	12.4
N	5	5	5	5	5	5	5	5	5	5	5	5

--: Data Unavailable

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 143 GROUP: 2-F SEX: FEMALE
DOSE: 0.5 (mg base/kg)

ANIMAL #	DAY 18	DAY 20
803	327	357
806	357	391
826	314	335
836	319	339
842	329	362
MEAN	329	357
S.D.	16.7	22.3
N	5	5

--: Data Unavailable

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 143 GROUP: 3-F SEX: FEMALE
DOSE: 1.0(mg base/kg)

ANIMAL #	DAY 0	DAY 4	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15
805	216	234	245	248	255	264	269	274	279	291	299	315
813	210	224	247	251	256	250	262	267	277	277	284	299
821	219	222	239	243	244	256	257	260	268	274	275	286
832	223	236	253	257	264	260	267	275	273	279	282	291
841	225	226	244	250	253	258	265	269	269	275	280	290
MEAN	219	228	246	250	254	258	264	269	273	279	284	296
S.D.	5.9	6.2	5.1	5.1	7.2	5.2	4.7	6.0	4.8	6.9	9.0	11.5
N	5	5	5	5	5	5	5	5	5	5	5	5

--: Data Unavailable

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 143 GROUP: 3-F SEX: FEMALE
DOSE: 1.0(mg base/kg)

ANIMAL #	DAY 18	DAY 20
805	354	388
813	332	357
821	319	341
832	315	340
841	329	351
MEAN	330	355
S.D.	15.2	19.6
N	5	5

--: Data Unavailable

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 143 GROUP: 4-F SEX: FEMALE
DOSE: 2.0(mg base/kg)

ANIMAL #	DAY 0	DAY 4	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15
801	223	228	245	250	259	266	275	280	281	288	298	306
802	219	236	257	259	264	271	271	281	282	283	297	307
827	218	233	258	264	271	280	283	291	302	305	311	317
835	203	213	237	247	249	257	267	267	278	284	298	300
839	221	225	240	245	255	260	264	266	273	281	287	298
MEAN	217	227	247	253	260	267	272	277	283	288	298	306
S.D.	7.9	8.9	9.7	8.2	8.4	9.1	7.4	10.5	11.1	9.7	8.5	7.4
N	5	5	5	5	5	5	5	5	5	5	5	5

--: Data Unavailable

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 143 GROUP: 4-F SEX: FEMALE
DOSE: 2.0(mg base/kg)

ANIMAL #	DAY 18	DAY 20
801	352	381
802	342	376
827	360	394
835	336	367
839	330	359
MEAN	344	375
S.D.	12.1	13.4
N	5	5

--: Data Unavailable

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 143 GROUP: 5-F SEX: FEMALE
DOSE: 4.0(mg base/kg)

ANIMAL #	DAY 0	DAY 4	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15
808	204	221	238	235	243	249	258	259	261	260	266	274
818	224	233	247	246	254	258	260	269	276	278	279	289
819	216	225	238	240	247	253	255	259	261	267	275	286
829	217	228	253	260	272	280	276	279	293	302	302	312
840	216	224	250	254	257	255	261	263	266	267	272	283
MEAN	215	226	245	247	255	259	262	266	271	275	279	289
S.D.	7.2	4.5	6.9	10.1	11.2	12.2	8.2	8.4	13.5	16.5	13.8	14.1
N	5	5	5	5	5	5	5	5	5	5	5	5

--: Data Unavailable

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 143 GROUP: 5-F SEX: FEMALE
DOSE: 4.0(mg base/kg)

ANIMAL #	DAY 18	DAY 20
808	313	336
818	334	368
819	328	351
829	355	377
840	315	335
MEAN	329	353
S.D.	17.0	18.8
N	5	5

--: Data Unavailable

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY STUDY OF WR242511 IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 143 GROUP: 6-F SEX: FEMALE
DOSE: 8.0(mg base/kg)

ANIMAL #	DAY 0	DAY 4	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15
809	209	228	247	248	246	240	242	235	235	232	238	243
811	219	232	249	252	251	238	239	248	248	234	241	255
828	--	--	--	--	--	--	--	--	--	--	--	--
831	209	218	234	229	229	226	231	232	232	232	231	236
823	211	219	242	245	238	249	249	243	244	250	247	261
MEAN	212	224	243	244	241	238	240	240	240	237	239	249
S.D.	4.8	6.8	6.7	10.1	9.6	9.5	7.5	7.3	7.5	8.7	6.7	11.3
N	4	4	4	4	4	4	4	4	4	4	4	4

--: Data Unavailable

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 143 GROUP: 6-F SEX: FEMALE
DOSE: 8.0(mg base/kg)

ANIMAL #	DAY 18	DAY 20
809	292	331
811	312	344
828	--	--
831	279	298
823	312	343
MEAN	299	329
S.D.	16.2	21.5
N	4	4

--: Data Unavailable

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 143 GROUP: 1-F SEX: FEMALE
DOSE: 0(mg/kg)

ANIMAL #	DAY 7[b]	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15	DAY 18	DAY 20	TOTAL GAIN
807	0	8	0	9	9	7	7	6	13	38	33	130
810	3	8	7	12	4	9	5	3	16	32	30	129
812	5	5	8	-1	7	7	3	9	10	39	30	122
830	3	-1	0	12	5	3	6	10	8	32	28	106
837	8	6	2	3	11	10	6	14	10	41	31	142
MEAN	4	5	3	7	7	7	5	8	11	36	30	126
S.D.	2.9	3.7	3.8	5.8	2.9	2.7	1.5	4.2	3.1	4.2	1.8	13.2
N	5	5	5	5	5	5	5	5	5	5	5	5

--: Data Unavailable

a = Successive periods
b = Baseline is Day 6

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 143 GROUP: 2-F SEX: FEMALE
DOSE: 0.5(mg/kg)

ANIMAL #	DAY 7[b]	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15	DAY 18	DAY 20	TOTAL GAIN
803	3	8	13	3	6	1	3	11	7	32	30	117
806	6	11	9	9	6	7	9	2	7	42	34	142
826	4	6	5	8	4	2	6	9	-1	29	21	93
836	6	4	1	7	6	4	5	11	-1	31	20	94
842	8	0	3	7	8	4	5	10	9	24	33	111
MEAN	5	6	6	7	6	4	6	9	4	32	28	111
S.D.	1.9	4.1	4.8	2.3	1.4	2.3	2.2	3.8	4.8	6.6	6.7	20.1
N	5	5	5	5	5	5	5	5	5	5	5	5

--: Data Unavailable

a = Successive periods
b = Baseline is Day 6

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 143 GROUP: 3-F SEX: FEMALE
DOSE: 1.0(mg/kg)

ANIMAL #	DAY 7[b]	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15	DAY 18	DAY 20	TOTAL GAIN
805	3	7	9	5	5	5	12	8	16	39	34	143
813	4	5	-6	12	5	10	0	7	15	33	25	110
821	4	1	12	1	3	8	6	1	11	33	22	102
832	4	7	-4	7	8	-2	6	3	9	24	25	87
841	6	3	5	7	4	0	6	5	10	39	22	107
MEAN	4	5	3	6	5	4	6	5	12	34	26	110
S.D.	1.1	2.6	7.9	4.0	1.9	5.1	4.2	2.9	3.1	6.1	4.9	20.6
N	5	5	5	5	5	5	5	5	5	5	5	5

--: Data Unavailable

a = Successive periods
b = Baseline is Day 6

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY STUDY OF WR242511 IN RATS

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 143 GROUP: 4-F SEX: FEMALE
DOSE: 2.0(mg/kg)

ANIMAL #	DAY 7[b]	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15	DAY 18	DAY 20	TOTAL GAIN
801	5	9	7	9	5	1	7	10	8	46	29	136
802	2	5	7	0	10	1	1	14	10	35	34	119
827	6	7	9	3	8	11	3	6	6	43	34	136
835	10	2	8	10	0	11	6	14	2	36	31	130
839	5	10	5	4	2	7	8	6	11	32	29	119
MEAN	6	7	7	5	5	6	5	10	7	38	31	128
S.D.	2.9	3.2	1.5	4.2	4.1	5.0	2.9	4.0	3.6	5.9	2.5	8.6
N	5	5	5	5	5	5	5	5	5	5	5	5

--: Data Unavailable

a = Successive periods
b = Baseline is Day 6

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 143 GROUP: 5-F SEX: FEMALE
DOSE: 4.0(mg/kg)

ANIMAL #	DAY 7 [b]	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15	DAY 18	DAY 20	TOTAL GAIN
808	-3	8	6	9	1	2	-1	6	8	39	23	98
818	-1	8	4	2	9	7	2	1	10	45	34	121
819	2	7	6	2	4	2	6	8	11	42	23	113
829	7	12	8	-4	3	14	9	0	10	43	22	124
840	4	3	-2	6	2	3	1	5	11	32	20	85
MEAN	2	8	4	3	4	6	3	4	10	40	24	108
S.D.	4.0	3.2	3.8	4.9	3.1	5.1	4.0	3.4	1.2	5.1	5.5	16.4
N	5	5	5	5	5	5	5	5	5	5	5	5

--: Data Unavailable

a = Successive periods
b = Baseline is Day 6

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 143 GROUP: 6-F SEX: FEMALE
DOSE: 8.0(mg/kg)

ANIMAL #	DAY 7[b]	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15	DAY 18	DAY 20	TOTAL GAIN
809	1	-2	-6	2	-7	0	-3	6	5	49	39	84
811	3	-1	-13	1	9	0	-14	7	14	57	32	95
828	--	--	--	--	--	--	--	--	--	--	--	--
831	-5	0	-3	5	1	0	0	-1	5	43	19	64
823	3	-7	11	0	-6	1	6	-3	14	51	31	101
MEAN	1	-3	-3	2	-1	0	-3	2	10	50	30	86
S.D.	3.8	3.1	10.1	2.2	7.4	0.5	8.4	5.0	5.2	5.8	8.3	16.3
N	4	4	4	4	4	4	4	4	4	4	4	4

--: Data Unavailable

a = Successive periods
b = Baseline is Day 6

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 143 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg base/kg)

ANIMAL #	DAY 10[b]	DAY 15	DAY 20
807	21	24	25
810	21	23	26
812	18	22	24
830	18	22	23
837	19	26	27
MEAN	19	23	25
S.D.	1.5	1.7	1.6
N	5	5	5

--: Data Unavailable

a = Successive periods

b = Baseline is Day 6

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RATS

INDIVIDUAL DAILY FOOD CONSUMPTION[a] (Grams)

STUDY: 143 GROUP: 2-F SEX: FEMALE
DOSE: 0.5 (mg base/kg)

ANIMAL #	DAY 10[b]	DAY 15	DAY 20
803	23	22	25
806	23	25	28
826	19	24	26
836	18	23	23
842	19	22	19
MEAN	20	23	24
S.D.	2.4	1.3	3.4
N	5	5	5

--: Data Unavailable

a = Successive periods

b = Baseline is Day 6

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY STUDY OF WR242511 IN RATS

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 143 GROUP: 3-F SEX: FEMALE
DOSE: 1.0 (mg base/kg)

ANIMAL #	DAY 10[b]	DAY 15	DAY 20
805	20	25	30
813	19	23	25
821	19	22	25
832	17	23	21
841	18	22	24
MEAN	19	23	25
S.D.	1.1	1.2	3.2
N	5	5	5

--: Data Unavailable

a = Successive periods

b = Baseline is Day 6

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 143 GROUP: 4-F SEX: FEMALE
DOSE: 2.0 (mg base/kg)

ANIMAL #	DAY 10[b]	DAY 15	DAY 20
801	22	23	27
802	20	23	27
827	20	24	25
835	20	28	28
839	20	25	26
MEAN	20	25	27
S.D.	0.9	2.1	1.1
N	5	5	5

--: Data Unavailable

a = Successive periods

b = Baseline is Day 6

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY STUDY OF WR242511 IN RATS

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 143 GROUP: 5-F SEX: FEMALE
DOSE: 4.0(mg base/kg)

ANIMAL #	DAY 10[b]	DAY 15	DAY 20
808	15	18	25
818	18	20	25
819	17	19	25
829	22	24	29
840	17	19	23
MEAN	18	20	25
S.D.	2.6	2.3	2.2
N	5	5	5

--: Data Unavailable

a = Successive periods

b = Baseline is Day 6

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY STUDY OF WR242511 IN RATS

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 143 GROUP: 6-F SEX: FEMALE
DOSE: 8.0 (mg base/kg)

ANIMAL #	DAY 10[b]	DAY 15	DAY 20
809	14	12	25
811	12	13	25
828	--	--	--
831	10	12	20
823	17	20	30
MEAN	13	14	25
S.D.	3.0	3.9	4.1
N	4	4	4

--: Data Unavailable

a = Successive periods

b = Baseline is Day 6

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RATS

INDIVIDUAL ORGAN WEIGHTS

STUDY: 143
SEX: FEMALE

GROUP: 1-F - 0 mg base/kg
ALL FATES ALL DAYS ALL BALANCES

ANIMAL ID: / BALANCE NO.:	807	810	812	830	837
BODY WEIGHT (G)	378	360	367	346	392
GRAVID UTERUS (G)	80.26	71.69	73.21	64.74	75.61
% BODY WEIGHT	21.233	19.914	19.948	18.711	19.288

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RATS

INDIVIDUAL ORGAN WEIGHTS

STUDY: 143
SEX: FEMALE

GROUP: 2-F - 0.5 mg base/kg
ALL FATES ALL DAYS ALL BALANCES

ANIMAL ID: / BALANCE NO.:	803	806	826	836	842
BODY WEIGHT (G)	357	391	335	339	362
GRAVID UTERUS (G)	61.23	81.88	40.51	51.65	67.81
% BODY WEIGHT	17.151	20.941	12.093	15.236	18.732

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RATS

INDIVIDUAL ORGAN WEIGHTS

STUDY: 143
SEX: FEMALE

GROUP: 3-F - 1 mg base/kg
ALL FATES ALL DAYS ALL BALANCES

ANIMAL ID: / BALANCE NO.:	805	813	821	832	841
BODY WEIGHT (G)	388	357	341	340	351
GRAVID UTERUS (G)	73.11	65.40	57.65	68.04	69.21
% BODY WEIGHT	18.843	18.319	16.906	20.012	19.718

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DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RATS

INDIVIDUAL ORGAN WEIGHTS

STUDY: 143
SEX: FEMALE

GROUP: 4-F - 2 mg base/kg
ALL FATES ALL DAYS ALL BALANCES

ANIMAL ID: / BALANCE NO.:	801	802	827	835	839
BODY WEIGHT (G)	381	376	394	367	359
GRAVID UTERUS (G)	73.26	74.74	65.04	61.22	67.11
% BODY WEIGHT	19.228	19.878	16.508	16.681	18.694

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY
STUDY OF WR242511 IN RATS

INDIVIDUAL ORGAN WEIGHTS

STUDY: 143
SEX: FEMALE

GROUP: 5-f - 4 mg base/kg

	ALL FATES	ALL DAYS	ALL BALANCES		
ANIMAL ID:	808	818	819	829	840
BALANCE NO.:					
BODY WEIGHT (G)	336	368	351	377	335
GRAVID UTERUS (G)	66.10	--	64.19	66.98	72.33
% BODY WEIGHT	19.673	--	18.288	17.767	21.591

(--)-Data Unavailiable (uterus inadvertently not weighed)

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY STUDY OF WR242511 IN RATS

Individual Maternal Cesarean Section Data

Dose Level (mg base/kg/day)	Dam No.	Total Implantations	*Corpora Lutea*	Resorptions		Viable Fetuses per Dam	Non-Viable Fetuses per Dam	Gross Dam Observations
				Early	Late			
0.0	837	13	17	0	0	13	0	Normal
	830	11	18	0	0	11	0	Normal
	810	13	12	1	0	12	0	Normal
	812	15	15	2	0	13	0	Normal
	807	13	18	0	0	13	0	Normal
0.5	826	11	15	4	0	7	0	Normal
	836	11	17	1	0	10	0	Normal
	842	12	14	0	0	12	0	Normal
	806	13	18	2	0	13	0	Normal
	803	13	16	2	0	11	0	Normal
1.0	832	12	16	0	0	12	0	Normal
	841	14	16	1	0	13	0	Normal
	821	11	13	1	0	10	0	Normal
	813	13	16	1	0	12	0	Normal
	805	13	18	1	0	12	0	Normal

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY STUDY OF WR242511 IN RATS

Individual Maternal Cesarean Section Data

Dose Level (mg base/kg/day)	Dam No.	Pre-implantation Loss %	Post-implantation Loss %	Total Loss / Litter %
0.0	837	24	0	24
	830	39	0	39
	810	-8	8	0
	812	0	13	13
	807	28	0	28
0.5	826	27	36	53
	836	35	9	41
	842	14	0	14
	806	28	0	28
	803	19	15	31
1.0	832	25	0	25
	841	13	7	19
	821	15	9	23
	813	19	8	25
	805	28	8	33

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY STUDY OF WR242511 IN RATS

Individual Maternal Cesarean Section Data

Dose Level (mg base/kg/day)	Dam No.	Total Implantations	*Corpora Lutea*	Resorptions		Viable Fetuses per Dam	Non-Viable Fetuses per Dam	Gross Dam Observations
				Early	Late			
2.0	835	12	15	1	0	11	0	Normal
	827	12	18	1	0	11	0	Normal
	839	13	16	2	0	11	0	Normal
	801	13	17	1	0	12	0	Normal
	802	13	18	0	0	13	0	Normal
4.0	829	12	16	0	0	12	0	Normal
	840	12	16	0	0	12	0	Normal
	819	12	20	0	0	12	0	Normal
	808	12	11	0	0	12	0	Normal
	818	15	NA	1	0	14	0	Normal
8.0	823	14	15	1	0	13	0	Normal
	831	12	14	3	0	9	0	Normal
	811	14	20	0	0	14	0	Normal
	809	13	15	0	0	13	0	Normal

NA= Data Not Available.

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY STUDY OF WR242511 IN RATS

Individual Maternal Cesarean Section Data

Dose Level (mg base/kg/day)	Dam No.	Pre-implantation Loss %	Post-implantation Loss %	Total Loss / Litter %
2.0	835	20	8	27
	827	33	8	39
	839	19	15	31
	801	24	8	29
	802	28	0	28
4.0	829	25	0	25
	840	25	0	25
	819	40	0	40
	808	-9	0	-9
	818	NA	7	NA
8.0	823	7	7	13
	831	14	25	36
	811	30	0	30
	809	13	0	13

NA = Data Not available

APPENDIX 2

INDIVIDUAL FETAL DATA

- Fetal Observations
- Individual Body Weights

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-7Q
Study No.: 143

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RATS

List of Abbreviations

NA = Not applicable N = No visible abnormalities A = Alive D = Dead	R = Right L = Left M = Male F = Female H = Head B= Back	NK = Neck HL = Hind limb FL = Fore limb DI = Digit SC = Scalp TR = Trunk	PT = Protruded tongue SB = Spina bifida SUBQ = Subcutaneous P = Petechial ABD = Abdominal	CP = Cleft palate CL = Cleft lip HT = Hematoma EX = Exophthalmos AN = Anophthalmos EC = Exencephaly MI = Microcephaly

Note: Fetal animal numbers in the body weight table are expressed as the dam animal number followed by the implantation site. For example: Fetus number 1234 = dam number 123, implantation site no.4

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RATS
FETAL OBSERVATIONS DOSE (0.0 mg base/kg)

Dam No.	Date Sac	Implantation Sites	Sex	Status	Fetal Body Wt. (g)	External Examination
837	5/6/94	1	F	A	3.68	N
		2	F	A	3.63	N
		3	F	A	3.96	N
		4	F	A	3.74	N
		5	M	A	4.11	N
		6	M	A	4.00	N
		7	M	A	4.08	SUBQ HT Anterior ABD
		8	M	A	3.83	N
		9	M	A	4.01	N
		10	F	A	3.67	N
		11	M	A	2.91	SUBQ HT NK
		12	M	A	3.74	N
		13	F	A	3.30	N
830	5/6/94	1	M	A	3.85	SUBQ HT L ear
		2	M	A	3.96	N
		3	M	A	3.69	SUBQ P(3) HT TR
		4	F	A	3.78	SUBQ HT TR
		5	F	A	4.22	SUBQ HT L ear & L thigh
		6	F	A	3.86	N
		7	F	A	3.78	N
		8	M	A	3.64	SUBQ HT TR
		9	M	A	4.06	SUBQ HT R thigh
		10	M	A	3.84	N
		11	M	A	3.55	N
810	5/5/94	1	F	A	4.13	N
		2	M	A	3.65	N
		3	F	A	3.89	N
		4	F	A	4.33	N
		5	F	A	4.26	N
		6	F	A	4.46	N
		7	M	A	4.56	N
		8	M	A	4.47	N
		9	F	A	4.13	SUBQ P(1) HT SC
		10	F	A	4.10	SUBQ P(1) HT TR
		11	F	A	3.77	SUBQ P(1) HT TR
		12	-	ER	-	Early Resorption
		13	M	A	3.99	SUBQ P(1) HT TR
812	5/5/94	1	F	A	3.52	SUBQ HT R HL & SUBQ P(1) HT TR
		2	F	A	3.78	SUBQ HT chin
		3	F	A	3.82	N
		4	F	A	3.79	N
		5	M	A	3.95	SUBQ P(1) HT TR
		6	-	ER	-	Early Resorption
		7	M	A	3.88	N
		8	F	A	3.71	N
		9	M	A	3.90	N
		10	F	A	3.66	N
		11	-	ER	-	Early Resorption
		12	M	A	3.95	N
		13	F	A	3.60	SUBQ HT R face & R shoulder
		14	M	A	3.90	N
		15	M	A	3.93	N
807	5/5/94	1	F	A	3.94	N
		2	F	A	4.36	N
		3	F	A	4.29	SUBQ HT R HL
		4	M	A	4.16	N
		5	F	A	4.43	SUBQ HT R HL
		6	F	A	4.02	N
		7	M	A	4.29	SUBQ HT L HL
		8	M	A	4.14	N
		9	M	A	4.10	SUBQ P(3) HT TR
		10	M	A	3.96	N
		11	M	A	4.07	N
		12	F	A	3.81	SUBQ HT R HL
		13	M	A	3.95	SUBQ HT L TR

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RATS
DOSE (0.5 mg base/kg)

Dam No.	Date Sac	Implantation Site	Sex	Status	Fetal Body Wt. (g)	External Examination
826	5/6/94	1	-	ER	-	Early Resorption
		2	M	A	3.59	SU8Q HT R chin/upper lip
		3	F	A	3.77	N
		4	-	ER	-	Early Resorption
		5	F	A	3.63	N
		6	-	ER	-	Early Resorption
		7	M	A	3.54	N
		8	M	A	3.85	N
		9	F	A	3.69	N
		10	-	ER	-	Early Resorption
		11	M	A	3.80	N
836	5/6/94	1	F	A	3.00	SU8Q HT snout
		2	F	A	3.31	N
		3	F	A	3.11	SU8Q HT snout, L face, L groin , SC &P(4) HT TR
		4	M	A	3.40	SU8Q P(4) HT TR
		5	F	A	2.97	SU8Q HT L face & L groin
		6	M	A	3.40	N
		7	M	A	3.38	SU8Q P(1) HT TR
		8	M	A	3.05	N
		9	-	ER	-	Early Resorption
		10	M	A	3.12	N
		11	M	A	3.05	N
842	5/6/94	1	M	A	3.96	N
		2	F	A	3.82	N
		3	M	A	4.17	N
		4	M	A	3.98	N
		5	M	A	3.79	N
		6	F	A	3.66	N
		7	F	A	4.11	N
		8	M	A	4.21	N
		9	F	A	3.29	N
		10	F	A	3.85	N
		11	F	A	3.81	N
		12	F	A	3.56	SU8Q HT snout
806	5/5/94	1	M	A	4.17	N
		2	M	A	4.63	N
		3	F	A	4.07	N
		4	M	A	4.22	N
		5	M	A	4.40	SU8Q HT chin
		6	F	A	4.21	N
		7	M	A	4.67	N
		8	-	ER	-	Early Resorption
		9	F	A	4.41	N
		10	F	A	3.91	SU8Q HT(2) L FL
		11	F	A	4.08	N
		12	-	ER	-	Early Resorption
		13	F	A	4.54	N
		14	M	A	4.40	N
		15	F	A	4.10	N
803	5/5/94	1	F	A	3.47	N
		2	M	A	3.61	N
		3	-	ER	-	Early Resorption
		4	F	A	3.48	N
		5	M	A	3.80	N
		6	M	A	3.60	N
		7	-	ER	-	Early Resorption
		8	M	A	3.61	N
		9	M	A	3.78	N
		10	M	A	3.90	N
		11	M	A	3.89	N
		12	M	A	3.92	SU8Q P(2) HT L HL
		13	F	A	3.42	SU8Q HT L FL

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RATS
DOSE (1.0 mg base/kg)

Dam No.	Date Sac	Implantation Site	Sex	Status	Fetal Body Wt. (g)	External Examination
832	5/6/94	1	F	A	3.47	SU8Q HT R HL
		2	M	A	4.00	N
		3	M	A	3.90	N
		4	M	A	3.76	N
		5	F	A	3.85	N
		6	M	A	4.02	N
		7	M	A	3.87	N
		8	M	A	3.72	N
		9	M	A	3.83	N
		10	F	A	3.46	N
		11	M	A	3.72	N
		12	F	A	3.46	N
841	5/6/94	1	F	A	3.14	SU8Q HT L groin & R HL
		2	M	A	3.67	N
		3	-	ER	-	Early Resorption
		4	F	A	3.60	N
		5	M	A	3.77	N
		6	M	A	4.00	N
		7	F	A	3.93	N
		8	M	A	3.48	N
		9	M	A	3.19	N
		10	F	A	3.42	N
		11	M	A	3.36	SU8Q HT Anterior A8D
		12	F	A	3.20	N
		13	M	A	3.52	SU8Q HT chin
		14	M	A	2.88	N
821	5/5/94	1	-	ER	-	Early Resorption
		2	M	A	3.34	SU8Q HT snout & P(1) HT TR
		3	M	A	3.73	N
		4	F	A	4.02	N
		5	F	A	3.96	N
		6	M	A	4.39	N
		7	F	A	3.99	N
		8	M	A	3.87	N
		9	F	A	3.61	N
		10	M	A	3.59	SU8Q P(1) HT TR
		11	M	A	3.85	N
813	5/5/94	1	M	A	3.09	N
		2	M	A	2.98	SU8Q HT TR & A8D
		3	M	A	3.61	N
		4	F	A	3.49	N
		5	F	A	3.28	N
		6	F	A	3.37	N
		7	F	A	3.12	N
		8	M	A	3.76	N
		9	-	ER	-	Early Resorption
		10	F	A	3.19	N
		11	M	A	3.44	SU8Q P(4) HT TR
		12	M	A	3.15	N
		13	F	A	3.21	N
805	5/5/94	1	M	A	3.59	SU8Q HT R HL
		2	F	A	3.87	N
		3	F	A	3.86	N
		4	M	A	3.92	SU8Q P(6) TR
		5	F	A	3.51	SU8Q HT A8D
		6	M	A	4.43	N
		7	F	A	3.77	SU8Q P(2) HT TR
		8	F	A	3.88	N
		9	-	ER	-	Early Resorption
		10	M	A	3.70	SU8Q P(4) HT TR & HT R NK
		11	F	A	3.52	SU8Q HT around mouth
		12	F	A	3.85	SU8Q HT A8D
		13	M	A	4.05	SuU8Q HT A8D & P(1) TR

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RATS
DOSE (2.0 mg base/kg)

Dam No.	Date Sac	Implantation Site	Sex	Status	Fetal Body Wt. (g)	External Examination
835	5/6/94	1	M	A	3.75	N
		2	F	A	3.25	N
		3	M	A	3.42	N
		4	M	A	3.67	N
		5	M	A	3.72	SU8Q P(1) HT TR
		6	F	A	3.81	SU8Q P(1) HT TR
		7	M	A	3.78	N
		8	-	ER	-	Early Resorption
		9	M	A	3.77	N
		10	F	A	3.58	N
		11	M	A	3.79	N
		12	F	A	2.93	SU8Q P(1) HT behind ear, SC & snout
827	5/6/94	1	F	A	3.82	N
		2	F	A	3.22	N
		3	F	A	4.02	N
		4	-	ER	-	Early Resorption
		5	M	A	4.29	N
		6	M	A	4.00	N
		7	M	A	4.15	N
		8	F	A	3.91	N
		9	F	A	3.75	N
		10	M	A	4.24	N
		11	M	A	3.95	N
		12	F	A	4.03	N
839	5/6/94	1	M	A	4.10	N
		2	F	A	4.28	N
		3	-	ER	-	Early Resorption
		4	F	A	4.06	N
		5	M	A	3.91	SU8Q HT both HL
		6	M	A	3.96	N
		7	F	A	4.02	N
		8	F	A	4.15	N
		9	M	A	4.16	N
		10	F	A	3.86	N
		11	F	A	2.91	N
		12	-	ER	-	Early Resorption
		13	F	A	3.51	N
801	5/5/94	1	F	A	4.18	N
		2	F	A	3.97	N
		3	M	A	4.21	N
		4	F	A	4.09	N
		5	M	A	3.92	N
		6	M	A	3.74	SU8Q P(3) HT TR
		7	F	A	3.54	SU8Q HT R HL
		8	M	A	4.06	N
		9	-	ER	-	Early Resorption
		10	M	A	4.36	N
		11	F	A	4.00	N
		12	M	A	3.98	N
		13	F	A	4.08	N
802	5/5/94	1	M	A	3.27	SU8Q P(2) HT TR
		2	F	A	3.34	N
		3	M	A	4.19	N
		4	F	A	3.66	N
		5	F	A	3.87	N
		6	F	A	3.94	SU8Q HT R HL
		7	F	A	4.17	N
		8	F	A	4.05	N
		9	M	A	4.05	N
		10	F	A	4.00	N
		11	F	A	3.64	N
		12	F	A	3.66	N
		13	M	A	3.37	N

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RATS
DOSE (4.0 mg base/kg)

Dam No.	Date Sac	Implantation Site	Sex	Status	Fetal Body Wt. (g)	External Examination
829	5/6/94	1	F	A	3.72	N
		2	F	A	3.64	N
		3	F	A	3.93	N
		4	F	A	3.64	N
		5	M	A	4.06	N
		6	F	A	3.76	N
		7	F	A	3.84	N
		8	F	A	3.35	N
		9	F	A	3.65	N
		10	M	A	3.85	SU8Q HT snout
		11	M	A	3.97	SU8Q HT L groin
		12	F	A	3.40	SU8Q HT Anterior R ear
840	5/6/94	1	M	A	4.34	N
		2	M	A	3.95	N
		3	F	A	3.66	SU8Q HT lower jaw
		4	M	A	4.19	SU8Q HT NK
		5	M	A	4.16	N
		6	M	A	3.78	N
		7	F	A	3.95	N
		8	M	A	4.28	N
		9	F	A	4.20	N
		10	M	A	4.01	N
		11	M	A	4.03	N
		12	M	A	4.06	N
819	5/5/94	1	M	A	3.53	N
		2	F	A	3.25	N
		3	M	A	3.50	SU8Q P(1) HT TR
		4	M	A	3.60	N
		5	M	A	3.60	SU8Q P(1) HT TR and snout
		6	M	A	3.69	SU8Q P(1) HT TR and chin
		7	M	A	3.57	N
		8	M	A	3.59	N
		9	F	A	3.60	N
		10	F	A	3.58	SU8Q HT(2) R FL & SUBQ HT(2) TR
		11	F	A	4.20	N
		12	F	A	3.13	N
808	5/5/94	1	F	A	3.52	SU8Q HT chin
		2	M	A	3.67	N
		3	M	A	3.58	N
		4	F	A	3.81	N
		5	F	A	3.55	N
		6	F	A	3.67	N
		7	F	A	3.34	SU8Q HT chin
		8	M	A	3.18	N
		9	M	A	3.60	SU8Q P(1) HT R FL
		10	M	A	3.97	N
		11	F	A	3.62	N
		12	F	A	3.29	N
818	5/5/94	1	F	A	3.80	N
		2	M	A	3.71	N
		3	F	A	3.43	N
		4	M	A	4.19	N
		5	M	A	4.08	N
		6	F	A	3.22	N
		7	F	A	4.11	N
		8	F	A	4.05	N
		9	F	A	3.47	N
		10	-	ER	-	Early Resorption
		11	F	A	3.69	N
		12	F	A	4.08	N
		13	F	A	3.79	N
		14	F	A	3.78	N
		15	M	A	4.19	SU8Q HT L FL

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RATS
DOSE (8.0 mg base/kg)

Dam No.	Date Sac	Implantation Site	Sex	Status	Fetal Body Wt. (g)	External Examination
823	5/6/94	1	M	A	3.96	N
		2	-	ER	-	Early Resorption
		3	F	A	4.02	N
		4	M	A	4.45	N
		5	F	A	4.09	N
		6	M	A	4.48	N
		7	M	A	4.08	N
		8	F	A	4.20	N
		9	F	A	4.32	N
		10	F	A	4.16	N
		11	F	A	4.28	N
		12	M	A	4.49	N
		13	M	A	4.27	N
		14	M	A	4.31	SUBQ HT NK
831	5/6/94	1	F	A	3.48	N
		2	F	A	3.43	SU8Q HT lower TR
		3	-	ER	-	Early Resorption
		4	M	A	3.43	N
		5	M	A	3.58	N
		6	-	ER	-	Early Resorption
		7	-	ER	-	Early Resorption
		8	F	A	3.38	N
		9	M	A	3.71	N
		10	M	A	3.69	N
		11	F	A	3.22	N
		12	F	A	3.03	N
828	Animal was not pregnant					
811	5/5/94	1	M	A	3.01	N
		2	M	A	3.43	N
		3	M	A	3.38	N
		4	F	A	3.02	N
		5	F	A	3.14	N
		6	M	A	3.42	N
		7	F	A	2.89	N
		8	M	A	2.81	N
		9	M	A	3.18	N
		10	M	A	3.05	N
		11	M	A	3.38	N
		12	F	A	3.01	N
		13	M	A	3.01	N
		14	M	A	2.83	SU8Q P(2) HT TR
809	5/5/94	1	F	A	3.58	N
		2	F	A	3.51	N
		3	M	A	3.69	N
		4	M	A	4.03	N
		5	F	A	3.67	N
		6	M	A	3.73	N
		7	M	A	3.81	SU8Q HT L FL & behind R ear
		8	M	A	3.71	N
		9	M	A	3.89	N
		10	M	A	3.85	N
		11	F	A	3.48	SU8Q HT nose
		12	M	A	3.51	N
		13	F	A	3.43	N

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 143L GROUP: 1-M SEX: MALE
DOSE: 0 (mg base/kg)

ANIMAL #	DAY 20
8375	4.11
8376	4.00
8377	4.08
8378	3.83
8379	4.01
83711	2.91
83712	3.74
8301	3.85
8302	3.96
8303	3.69
8308	3.64
8309	4.06
83010	3.84
83011	3.55
8102	3.65
8107	4.56
8108	4.47
81013	3.99
8125	3.95
8127	3.88
8129	3.90
81214	3.90
81215	3.93
8074	4.16
8077	4.29
8078	4.14
8079	4.10
80710	3.96
80711	4.07
80713	3.95
81212	3.95
MEAN	3.94
S.D.	0.290
N	31

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 143L GROUP: 2-M SEX: MALE
DOSE: 0.5 (mg base/kg)

ANIMAL #	DAY 20
8262	3.59
8267	3.54
8268	3.85
82611	3.80
8364	3.40
8366	3.40
8367	3.38
8368	3.05
83610	3.12
83611	3.05
8421	3.96
8423	4.17
8424	3.98
8425	3.79
8428	4.21
8061	4.17
8062	4.63
8064	4.22
8065	4.40
8067	4.67
80614	4.40
8032	3.61
8035	3.80
8036	3.60
8038	3.61
8039	3.78
80310	3.90
80311	3.89
80312	3.92
MEAN	3.82
S.D.	0.430
N	29

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DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY STUDY OF WR242511 IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 143L GROUP: 3-M SEX: MALE
DOSE: 1.0(mg base/kg)

ANIMAL #	DAY 20
8322	4.00
8323	3.90
8324	3.76
8326	4.02
8327	3.87
8328	3.72
8329	3.83
83211	3.72
8412	3.67
8415	3.77
8416	4.00
8418	3.48
8419	3.19
84111	3.36
84113	3.52
8212	3.34
8213	3.73
8216	4.39
8218	3.87
82110	3.59
82111	3.85
8131	3.09
8132	2.98
8133	3.61
8138	3.76
81311	3.44
81312	3.15
8051	3.59
8054	3.92
8056	4.43
80510	3.70
80513	4.05
84114	2.88
MEAN	3.67
S.D.	0.360
N	33

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY STUDY OF WR242511 IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 143L GROUP: 4-M SEX: MALE
DOSE: 2.0 (mg base/kg)

ANIMAL #	DAY 20
8351	3.75
8353	3.42
8354	3.67
8355	3.72
8357	3.78
8359	3.77
83511	3.79
8275	4.29
8276	4.00
8277	4.15
82710	4.24
82711	3.95
8391	4.10
8395	3.91
8396	3.96
8399	4.16
8013	4.21
8015	3.92
8016	3.74
8018	4.06
80110	4.36
80112	3.98
8021	3.27
8023	4.19
8029	4.05
80213	3.37
MEAN	3.92
S.D.	0.281
N	26

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY STUDY OF WR242511 IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 143L GROUP: 5-M SEX: MALE
DOSE: 4.0(mg base/kg)

ANIMAL #	DAY 20
8295	4.06
82910	3.85
82911	3.97
8401	4.34
8402	3.95
8404	4.19
8405	4.16
8406	3.78
8408	4.28
84010	4.01
84011	4.03
84012	4.06
8191	3.53
8193	3.50
8194	3.60
8195	3.60
8196	3.69
8197	3.57
8198	3.59
8082	3.67
8083	3.58
8088	3.18
8089	3.60
80810	3.97
8182	3.71
8184	4.19
8185	4.08
81815	4.19
MEAN	3.85
S.D.	0.290
N	28

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY STUDY OF WR242511 IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 143L GROUP: 6-M SEX: MALE
DOSE: 8.0(mg base/kg)

ANIMAL #	DAY 20
8231	3.96
8234	4.45
8236	4.48
8237	4.08
82312	4.49
82313	4.27
82314	4.31
8314	3.43
8315	3.58
8319	3.71
83110	3.69
8111	3.01
8112	3.43
8113	3.38
8116	3.42
8118	2.81
8119	3.18
81110	3.05
81111	3.38
81113	3.01
81114	2.83
8093	3.69
8094	4.03
8096	3.73
8097	3.81
8098	3.71
8099	3.89
80910	3.85
80912	3.51
MEAN	3.66
S.D.	0.482
N	29

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY STUDY OF WR242511 IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 143L GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg base/kg)

ANIMAL #	DAY 20
8371	3.68
8372	3.63
8373	3.96
8374	3.74
83710	3.67
83713	3.30
8304	3.78
8305	4.22
8306	3.86
8307	3.78
8101	4.13
8103	3.89
8104	4.33
8105	4.26
8106	4.46
8109	4.13
81010	4.10
81011	3.77
8121	3.52
8122	3.78
8123	3.82
8124	3.79
8128	3.71
81210	3.66
81213	3.60
8071	3.94
8072	4.36
8073	4.29
8075	4.43
8076	4.02
80712	3.81
MEAN	3.92
S.D.	0.289
N	31

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY STUDY OF WR242511 IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 143L GROUP: 2-F SEX: FEMALE
DOSE: (mg base/kg)

ANIMAL #	DAY 20
8263	3.77
8265	3.63
8269	3.69
8361	3.00
8362	3.31
8363	3.11
8365	2.97
8422	3.82
8426	3.66
8427	4.11
8429	3.29
84210	3.85
84211	3.81
84212	3.56
8063	4.07
8066	4.21
8069	4.41
80610	3.91
80611	4.08
80613	4.54
80615	4.10
8031	3.47
8034	3.48
80313	3.42
MEAN	3.72
S.D.	0.420
N	24

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY STUDY OF WR242511 IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 143L GROUP: 3-F SEX: FEMALE
DOSE: 1.0 (mg base/kg)

ANIMAL #	DAY 20
8321	3.47
8325	3.85
83210	3.46
83212	3.46
8411	3.14
8414	3.60
8417	3.93
84110	3.42
84112	3.20
8214	4.02
8215	3.96
8217	3.99
8219	3.61
8134	3.49
8135	3.28
8136	3.37
8137	3.12
81310	3.19
81313	3.21
8052	3.87
8053	3.86
8055	3.51
8057	3.77
8058	3.88
80511	3.52
80512	3.85
MEAN	3.58
S.D.	0.291
N	26

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY STUDY OF WR242511 IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 143L GROUP: 4-F SEX: FEMALE
DOSE: 2.0 (mg base/kg)

ANIMAL #	DAY 20
8352	3.25
8356	3.81
83510	3.58
83512	2.93
8271	3.82
8272	3.22
8273	4.02
8278	3.91
8279	3.75
82712	4.03
8392	4.28
8394	4.06
8397	4.02
8398	4.15
83910	3.86
83911	2.9
83913	3.51
8011	4.18
8012	3.97
8014	4.09
8017	3.54
80111	4.00
80113	4.08
8022	3.34
8024	3.66
8025	3.87
8026	3.94
8027	4.17
8028	4.05
80210	4.00
80211	3.64
80212	3.66
MEAN	3.79
S.D.	0.354
N	32

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DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY STUDY OF WR242511 IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 143L GROUP: 5-F SEX: FEMALE
DOSE: 4.0 (mg base/kg)

ANIMAL #	DAY 20
8291	3.72
8292	3.64
8293	3.93
8294	3.64
8296	3.76
8297	3.84
8298	3.35
8299	3.65
82912	3.40
8403	3.66
8407	3.95
8409	4.20
8192	3.25
8199	3.60
81910	3.58
81911	4.20
81912	3.13
8081	3.52
8084	3.81
8085	3.55
8086	3.67
8087	3.34
80811	3.62
80812	3.29
8181	3.80
8183	3.43
8186	3.22
8187	4.11
8188	4.05
8189	3.47
81811	3.69
81812	4.08
81813	3.79
81814	3.78
MEAN	3.67
S.D.	0.279
N	34

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY STUDY OF WR242511 IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 143L GROUP: 6-F SEX: FEMALE
DOSE: 8.0 (mg base/kg)

ANIMAL #	DAY 20
8233	4.02
8235	4.09
8238	4.20
82310	4.16
82311	4.28
8311	3.48
8312	3.43
8318	3.38
83111	3.22
83112	3.03
8114	3.02
8115	3.14
8117	2.89
81112	3.01
8091	3.58
8092	3.51
8095	3.67
80911	3.48
80913	3.43
8239	4.32
MEAN	3.57
S.D.	0.463
N	20

APPENDIX 3

Protocol and Amendments

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-7Q
UIC/TRL Study No.: 143

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RATS

1.0 PURPOSE OF THE STUDY:

The purpose of this study is to provide information for use in the selection of dose levels for a developmental toxicity study of WR242511 in rats. The protocol for this study was approved by the UIC Animal Care Committee (Appendix 1).

2.0 SPONSOR:

2.1	Name:	U.S. Army Medical Materiel Development Activity
2.2	Address:	Fort Detrick Frederick, MD 21702-5009
2.3	Representative:	George J. Schieferstein, Ph.D.

3.0 TESTING FACILITY:

3.1	Name:	Toxicology Research Laboratory (TRL)
3.2	Address:	University of Illinois at Chicago (UIC) Department of Pharmacology 1940 W.Taylor St. Chicago, IL 60612-7353
3.3	Study Director:	Barry S. Levine, D.Sc., D.A.B.T.

4.0 DATES:

4.1	Proposed Initiation of In-Life Phase:	4/21/94
4.2	Proposed Completion of In-Life Phase:	5/06/94
4.3	Proposed Study Completion Date (Final Report):	7/06/94

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5.0 TEST ARTICLES

5.1 Name or Code No: WR242511 Tartrate
Bottle Number - BM05816

5.2 TRL Chemical No: 1720614

5.3 Physical Description: Yellow powder

5.4 Storage Conditions to Maintain Stability:

5.4.1 Temperature: -20 to -15°C.

5.4.2 Humidity: Ambient conditions at -20 to -15°C in a freezer.

5.4.3 Light: Protect from light.

5.4.4 Special Requirements: None.

5.5 Special Handling Procedures: Standard safety precautions will be followed including gloves, eye protection, mask, and lab coats.

5.6 Log of Test Article: The amount, date, identity of person(s) removing aliquots and the purpose for which each aliquot of the test article was removed from the batch will be documented. At termination of the study, unused test article may be returned to the Sponsor.

6.0 PERSONNEL:

Study Director	Barry S. Levine, D.Sc., D.A.B.T.
Reproductive Toxicologist	Ashraf F. Youssef, M.D., Ph.D.
Reproductive Scientist	Roberto A. Matamoros, D.V.M., Ph.D.
Clinical Veterinarian	James E. Artwohl, D.V.M., M.S., D.A.C.L.A.M.
Veterinarian Support	Documented in raw data
Analytical Chemist	Adam Negrusz, Ph.D.
Tox. Lab Supervisor	Soudabeh Soura, B.S.
Lead Technician	Documented in raw data
Chemistry Specialist	Thomas Tolhurst, B.S.

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7.0 TEST SYSTEM:

7.1 Species: Rat

7.2 Strain: CD® (Virus Antibody Free)

7.3 Sex(s)/Number: 30 timed-mated females

7.4 Age of Animals: 50 - 70 days old at study initiation.

7.5 Source of Animals: Charles River Breeding Laboratories, Inc. The specific source will be documented in the raw data.

7.6 Body Weight: Approximately 175 - 225 g at start of study.

7.7 Justification for Selection of Test System: The FDA requires the use of two animal species for preclinical developmental toxicity studies, typically the rat and rabbit. The CD® rat was selected for evaluation because; (1) it is one mammalian species accepted for use in embryo/fetal toxicity - teratogenicity studies; (2) this strain of rat has been demonstrated to be sensitive to developmental toxicants; (3) it has been used for nonclinical studies of developmental toxicity; (4) historical data and experience exist; and (5) it was specified by the Sponsor.

7.8 Procedure for Unique Identification of Test System: Each animal will be given a study unique number by the Supplier. This number will appear as an ear tag and will also appear on a cage card visible on the front of each cage. The cage card will additionally contain the study number, test article identifications, treatment group number and dose level. Cage cards will be color-coded as a function of treatment group. Raw data records and specimens will also be identified by the unique test animal number.

7.9 Housing: The animals will be housed in an AAALAC-accredited facility. Animals will be singly housed in polycarbonate cages with Anderson-bed-a-cob bedding (Heinold, Kankakee, Illinois) in a temperature (65-78°F) and humidity (30-70%) controlled room with a 14 hour light/10 hour dark cycle. The cage size, 840 cm^2 area and 20 cm height, is adequate to house rats at the upper weight range as described in the Guide for the *Care and Use of Laboratory Animals*, DHHS (NIH) No. 86.23. All animals will be routinely transferred to clean cages with fresh bedding once weekly.

7.10 Quarantine Procedure: Animals will be quarantined for at least 3 days during the time from receipt until dosing is initiated on Day 6 of gestation. During the quarantine period, the animals will be observed daily for signs of illness, and all unusual observations will be reported to the Study Director, Toxicologist or Clinical Veterinarian. Animals will be examined during quarantine and approved for use by the

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Clinical Veterinarian prior to being placed on test. Any sickly animals will be eliminated prior to the test animal selection process. If a selected animal appears sickly prior to initiation of treatment, it will be replaced by a healthy animal prior to initiation of treatment under the direction of the Study Director or Toxicologist. Quarantine release will be documented on the Clinical Veterinarian Log by the veterinarian prior to study initiation.

7.11 Food: Purina Certified Rodent Chow No. 5002 (Ralston Purina Company, St. Louis, MO) will be provided *ad libitum* from arrival until termination.

7.12 Water: Tap water from an automatic watering system in which the room distribution lines are flushed daily will be provided *ad libitum* from arrival until termination. The water is untreated with additional chlorine or HCl.

7.13 There are no known contaminants in the feed or water which are expected to influence the study. A copy of the feed certification will be kept with the study records. The results of bimonthly comprehensive chemical analyses of Chicago water are documented in files maintained by Quality Assurance.

7.14 It is not known if the animals will experience pain or distress during the study. Analgesic or anesthetic agents will confound the ability to determine the toxic potential of the test article, and therefore will not be used. If an animal is in severe pain or distress, following consultation with the veterinary staff, it will be euthanized in accordance with standard operating procedures.

8.0 EXPERIMENTAL DESIGN:

8.1 Treatment Groups:

Group No.	Dose Level (mg base/kg/day)	Number of Females*
1	0	5
2	0.5	5
3	1.0	5
4	2.0	5
5	4.0	5
6	8.0	5

* Presumed Pregnant

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Dose levels of WR242511 will be selected on the basis of a two week toxicity study in rat (UIC/TRL Study No. 106) and preliminary results of a thirteen week toxicity study in rats (UIC/TRL Study No. 107). The number of animals, 5/dose, is the number of animals typically used in preliminary dose range-finding developmental toxicity studies and is the number of animals indicated by the Sponsor in Task Order UIC-7, Modification 3.

8.2 Frequency and Route of Administration of Test Article: The test article will be administered once daily by gavage during days 6 - 15 of gestation, the period of major organogenesis. It will be given at a dosing volume of 5 ml/kg. The control group animals will receive the vehicle at the same dosing volume. The specific volume to be administered will be adjusted daily on the basis of body weight.

8.3 Justification of Route(s): The oral route is a convenient and accepted procedure for administering a specific amount of a test article to each animal. It mimics potential human exposure conditions and is specified by the Sponsor.

8.4 Procedure to Control Bias during the Assignment of Animals to Treatment Groups: During the quarantine/pretest period, animals judged to be suitable test subjects and meeting acceptable body weight requirements will be assigned to the study at random using a randomization procedure on the basis of body weight.

8.5 Test Article Vehicle: 1% Methylcellulose/0.2% Tween 80.

8.6 Test Article Dosage Form Preparation and Analyses: The dosage formulations for the test article will be prepared daily by diluting a stock formulation (made weekly) to appropriate concentration. Stability data obtained from a previous study (UIC/TRL Study No. 106) indicated that the dosing suspensions are stable for 48 hours at the dosage formulations being tested, and the stock formulation is stable for two weeks. Homogeneity data obtained from UIC/TRL Study No. 107 demonstrated that the test article suspensions are homogeneous (coefficients of variation for sampling in the top, middle and bottom of several test suspensions were typically less than 4%).

The stock test article suspension will be prepared by suspending the appropriate quantity of test article in the vehicle using a mortar and pestle. Stock and dosing suspensions will be stored at 0 - 4°C. Dosing suspensions will not be analyzed as this is a preliminary dose range-finding test and not a GLP compliant study.

8.7 Frequency of Observations, Test Analyses and Measurements:

8.7.1 Mortality Check: All animals will be observed twice daily, at least six hours apart for moribundity/mortality.

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8.7.2 Clinical Signs: All animals will be observed daily for clinical signs of toxicity approximately 1-2 hours after dosing, and in the morning after completion of the dosing period. Moribund animals will be sacrificed on that day and the uterine contents will be examined as described in Section 8.7.6.

8.7.3 Body Weights: Individual body weights will be recorded on day 0 of gestation (the day a vaginal plug is observed), on the day of randomization, and on gestation days 6 - 15, 18 and 20.

8.7.4 Food Consumption: Food consumption for all animals will be measured during the following intervals: days 6 - 10; 10 - 15; 15 - 20.

8.7.5 Sacrifice: On day 20 of presumed gestation, all surviving female rats will be euthanized by carbon dioxide asphyxiation followed immediately by cesarean section.

8.7.6 Cesarean-Sectioning Observations: The abdominal and thoracic cavities will be opened by a ventral midline incision and the contents examined. In gravid animals, the ovaries will be examined. The number of corpora lutea on each ovary will be recorded (ovaries discarded after evaluation). The gravid uterus will be examined and weighed. The number and location of viable and nonviable fetuses* *in utero*, early and late resorptions** and the total number of implantation sites will be recorded.

The uterine position of each fetus will be documented using the following procedure. All implantation sites, including resorptions, will be numbered in consecutive fashion beginning with the left distal uterine horn, noting the position of the cervix, and continuing from the proximal to the distal right uterine horn. Maternal tissues will only be saved for histopathological examination in 10% neutral buffered formalin as deemed necessary by the gross findings. The carcass of each dam will then be discarded.

*A viable fetus is defined as one which responds to stimuli. A non viable fetus is defined as a term fetus which does not respond to stimuli *in utero* or is not breathing.

**An early resorption is defined as one in which it is not grossly evident that organogenesis has occurred. A late resorption is defined as one in which it is grossly evident that organogenesis has occurred. A fetus with evident autolysis is considered a late resorption.

8.7.7 Confirmation of Pregnancy: Uteri from females that appear nongravid will be opened and placed for approximately 10 minutes in ammonium sulfide solution (0.5%) for detection of possible implantation sites. If implantation site is detected, the ovaries will be examined as in 8.7.6.

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8.7.8 Necropsy: Animals which die on test or are sacrificed if moribund will be examined as soon as possible for the cause of death. Examination will not be performed if precluded by postmortem autolysis. Pregnancy status and uterine contents will be recorded. Maternal tissues with gross lesions appropriate for retention may be fixed in neutral buffered 10% formalin for possible future evaluation as deemed necessary. Viscera which appear normal will be discarded. Naturally-delivered pups will be examined to the extent possible using the same methods described for fetuses.

8.7.9 Fetal Observations:

8.7.9.1 Body Weight and Sex: The number of fetuses will be recorded. Each fetus will be individually weighed and sexed.

8.7.9.2 Gross External Examination: All fetuses will be examined externally and each finding will be recorded. All fetuses will be euthanized by sodium pentobarbital (400 mg/ml; 4 g/kg; ≈0.01 ml/g I.P.). At the discretion of the Study Director or the Reproductive Toxicologist, fetuses with gross external alterations and other fetuses as deemed necessary may be preserved in Bouin's solution for possible future examination. All other fetuses will be discarded.

8.8 Statistical Analyses: The incidence of maternal and fetal observations will be determined, however statistical analyses may not be performed due to the small number of animals per group. If indicated, statistical analyses on a litter basis will be performed using nonparametric statistics such as log linear models, the Chi-square test, and/or Fisher's exact probability test. Fetal body weights, maternal body weights, weight gains, uterine absolute and relative weight (% body weight) and food consumption data will be analyzed by Analysis of variance tests. If a significant F ratio is obtained ($\rho \leq 0.05$), Dunnett's test will be used for pair-wise comparisions to the control group.

Quantitative data will be tabulated and presented in the report. In addition to the written report, summary data tables of parameters and variability will be transmitted to the Sponsor on magnetic media (computer diskette) in "ASCII" form. The transcribed data on disk will no longer be considered GLP compliant.

9.0 RECORDS TO BE MAINTAINED:

All data generated during the conduct of the study, except those that are generated as direct computer input, shall be recorded directly, promptly, and accurately in ink in bound books with prenumbered pages or on worksheets that shall be bound during or at the conclusion of the nonclinical laboratory study. All appropriate computer and machine output shall be bound during or at the conclusion of the study. All data entries shall be dated on the day of entry and signed or initialed by the person entering the data.

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Any changes in entries for whatever reason (e.g., to correct an error or transposition) shall be made so as not to obscure the original entry, shall indicate the reason for such change, and shall be dated and signed or identified at the time of data input. In computer driven collection systems, the operator responsible for direct data input shall be identified at the time of data input. Any changes in computer entries for whatever reason (e.g., to correct an error or transposition) shall be made in such a manner so as not to obscure the original entry, if possible, shall indicate the reason for such change, and shall be dated and the responsible individual shall be identified.

All recorded data shall be reviewed, signed, and dated by a knowledgeable person, other than the person making the entry, to assure adherence to procedures and to verify observations. Upon completion of the study and submission of the final report, all raw data, documentation, specimens, test article reserves and other materials necessary to reconstruct the study will be stored in the TRL archives maintained by Quality Assurance.

All changes or revisions, and reasons therefore, to this protocol once it is approved shall be documented, signed by the Study Director and Sponsor, dated and maintained with the protocol.

10.0 REGULATORY REQUIREMENTS:

This study will be performed within the spirit of the UIC/TRL Quality Assurance Program designed to conform with FDA Good Laboratory Practice Regulations and EPA Good Laboratory Practice Standards.

Will this study be submitted to a regulatory agency? Yes If so, to which agency(ies)? Food and Drug Administration
Does the Sponsor Request that test article samples be returned? Possibly; direction will be provided by the Sponsor.
Does the Sponsor request that samples of the test article/carrier mixture(s) be returned to the Sponsor? No

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DATE 12/16/93

11.0 PROTOCOL APPROVAL:

STUDY DIRECTOR: _____ 11/19/93
Barry S. Levine, D.Sc., D.A.B.T. Date

SPONSOR APPROVAL: _____ 12/13/93.
George J. Schieferstein, Ph.D. Date
Contracting Officer's
Representative (COR)

COMMENTS FROM THE COR:

UIC The University of Illinois at Chicago

Office of the Vice Chancellor for Research (M/C 672)
310 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227
(312) 996-4995

Appendix 1

November 22,1993

Barry S. Levine
Med-Pharmacology
312 BGRC, M/C 868

Dear Dr. Levine:

The protocol indicated below has been reviewed in accordance with the Animal Care Policies of the University of Illinois at Chicago and approved on July 20, 1993.

Title of Application: **Dose Range-Finding Developmental Toxicity Study of WR242511 In Rats**

ACC Number: 93-077-6

This institution has Animal Welfare Assurance Number A3460.01 on file with the Office for Protection from Research Risks, NIH. Please transmit this letter of acceptable verification of your research protocol to your sponsor.

Thank you for complying with the Animal Care Policies and Procedures of UIC.

Sincerely yours,

Josephine B. Miller

Josephine B. Miller, Ph.D.
Chair, Animal Care Committee

JBM:st
xc:BRL

PROTOCOL AMENDMENT

Study No.: 143

Title: Dose Range-Finding Developmental Toxicity Study of WR242511 in Rats

1. Page 2 Section 5.1

Indicate the Bottle Number of the test article; "BM05816".

Reason: Sponsor requested that the specific bottle number be included in the protocol.

2. Page 4 Section 7

Add the following section:

"7.14 It is not known if the animals will experience pain or distress during the study. Analgesic or anesthetic agents will confound the ability to determine the toxic potential of the test article, and therefore will not be used. If an animal is in severe pain or distress, following consultation with the veterinary staff, it will be euthanized in accordance with standard operating procedures."

Reason: Sponsor requested addition to the protocol.

3. Page 3 Section 7.4

Replace the numbers to read "50 - 70".

Reason: Mistake in the protocol

4. Page 3 Section 7.6

Replace the numbers to read "175 - 225 ".

Reason: Mistake in the protocol

5. Page 4 Section 7.10

Replace the first sentence to read "Animals will be quarantined for at least 3 days during the time of receipt until dosing is initiated on day 6 of gestation."

Reason: Clarification of the period of quarantine.

6. Page 4 Section 8.1

A. Indicate dose levels will also be selected based on preliminary results of a thirteen week toxicity study in rats (UIC/TRL Study No. 107).

B. Add the following sentence to the first paragraph "The number of animals, 5/dose level, is the number of animals typically used in preliminary dose range-finding developmental toxicity studies and is the number of animals indicated by the Sponsor in Task Order UIC-7, Modification 3."

PROTOCOL AMENDMENT

Study No.: 143

Title: Dose Range-Finding Developmental Toxicity Study of WR242511 in Rats

(6 contd.)
Reason: Sponsor requested additions to the protocol.

7. Page 5 Section 8.6

Change the text as follows to indicate that stability and homogeneity testing have been performed in previous toxicity studies; "The dosage formulations for the test article will be prepared daily by diluting a stock formulation (made weekly) to appropriate concentration. Stability data obtained from a previous study (UIC/TRL Study No. 106) indicated that the dosing suspensions are stable for 48 hours at the dosage formulations being tested, and the stock formulation is stable for two weeks. Homogeneity data obtained from UIC/TRL Study No. 107 demonstrated that the test article suspensions are homogeneous (coefficients of variation for sampling in the top, middle and bottom of several test suspensions were typically less than 4%).

The stock test article suspension will be prepared by suspending the appropriate quantity of test article in the vehicle using a mortar and pestle. Stock and dosing suspensions will be stored at 0 - 4°C. Dosing suspensions will not be analyzed as this is a preliminary dose range-finding test and not a GLP compliant study."

8. Page 7 Section 8.7.7

Add the following sentence: "If any implantation site is detected, the ovaries will be examined as in 8.7.6."

Reason: If pregnancy evidence is confirmed, ovarian changes should be examined.

Approvals:

STUDY DIRECTOR: _____ 12/10/93
Barry S. Levine, D.Sc. D.A.B.T. Date

SPONSOR APPROVAL: _____ 12/13/93.
George J. Schieferstein, Ph.D. Date
Contracting Officer's
Representative (COR)

PROTOCOL AMENDMENT

Study No.: 143

Title: Dose Range-Finding Developmental Toxicity Study of WR242511 in Rats

9. Page 1 Section 4.0

Change the section to reflect the following changes in dates.

4.1 Proposed Initiation of In-Life Phase: 4/21/94

4.2 Proposed Completion of In-Life Phase: 5/06/94

4.3 Proposed Study Completion Date (Final Report): 7/06/94

Reason: Dates were not decided at the time the protocol was submitted.

10. Page 3 Section 7.8

Change the first sentence to read, "Each animal will be given a study unique number by the Supplier", and Delete the second sentence.

Reason: Each animal will be assigned its study number on Day 0 of gestation (day of vaginal plug) by the supplier.

11. Page 4 Section 8.0

Change the dose levels to reflect the following.

Group No.	Dose Level (mg base/kg/day)
1	0
2	0.5
3	1.0
4	2.0
5	4.0
6	8.0

Reason: Doses were not decided upon at the time the protocol was submitted.

PROTOCOL AMENDMENT

Study No.: 143

Title: Dose Range-Finding Developmental Toxicity Study of WR242511 in Rats

12. Page 5 Section 8.4

In the last sentence, change "randomiation" to "randomization".

Reason: Typographical error.

13. Page 6 Section 8.7.2

In the last sentence, change "uteine" to "uterine".

Reason: Typographical error.

14. Page 6 Section 8.7.7

In the first sentence replace "appriximately" by "approximately".

Reason: Typographical error.

15. Page 7 Section 8.7.9.2

Change the second sentence as follows:

"All fetuses will be euthanized by sodium pentobarbital (400 mg/ml; 4g/kg; ~0.01 ml/g I.P.)."

Reason: Changed as requested by the Sponsor.

APPROVAL:

STUDY DIRECTOR: _____ 5/19/94
Barry S. Levine, D.Sc., D.A.B.T. Date

SPONSOR APPROVAL: _____ 5/19/94
George J. Schieferstein, Ph.D. Date
Contracting Officer's
Representative (COR)

APPENDIX 4

Study Deviations

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY STUDY OF WR242511 IN RATS

Study Deviations*

Deviation Type	Specific Deviation	Effect on Study
Protocol	Humidity was out of range in one occasion.	None; the deviation was minimal.

* The detailed "Deviation Reports" are contained in the raw data which are archived at the University of Illinois at Chicago, Department of Pharmacology, Chicago, Illinois.

The above deviation did not affect the integrity of the study.

Barry S. Levine, D.Sc., D.A.B.T.

Date